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Metabolic Interference and the + − Heterozygote. A Hypothetical Form of Simple Inheritance Which Is neither Dominant nor Recessive

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SUMMARY

Another form of simple inheritance is possible which is neither dominant nor recessive and in which the heterozygote alone is affected. In this system, homozygosity for the normal allele AA, and the mutant allele $A'A'$, give a normal phenotype. Only the heterozygous condition AA' (+ − heterozygote) produces an abnormal phenotype because the two alleles, when present together, interact to produce a harmful effect. This metabolic interference may occur because the two allelic genes code for different subunits of a multisubunit enzyme or structural protein. The two genes may interact in other ways and need not be allelic.

The various matings result in pedigrees, which in some cases resemble those of dominant or recessive inheritance, and in other cases are unique. Certain unusual pedigrees in the literature are compatible with the predictions of metabolic interference and are difficult to explain by other means. Metabolic interference is most likely to be recognized as: (1) a disorder limited to females, apparently dominant or recessive, especially a disorder passed to affected females through unaffected males; (2) a disorder occurring in all members of a large sibship with normal parents; (3) a disorder occurring in all members of a large sibship with one parent similarly affected; (4) an apparently dominant disorder with females more severely affected than males; (5) an apparently X-linked dominant disorder in which males are not more severely affected; or (6) any autosomal dominant disorder.

Examples of possible metabolic interference exist among disorders of animals, and the mechanism could be a factor in speciation. Tissue culture methods could be used to demonstrate metabolic interference.

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DOMINANT AND RECESSIVE INHERITANCE

Two kinds of simple inheritance are generally recognized in humans: dominant and recessive. The essential distinguishing feature is the gene dose effect upon the phenotype.

A recessive trait requires a double gene dose for expression in the phenotype. A single gene dose of a recessive gene gives a phenotype indistinguishable from the normal one; that is, the trait is expressed in the homozygote but not in the heterozygote. Phenotype here is defined clinically, not biochemically.

A dominant trait is expressed in the phenotype with either a single or double gene dose; that is, the trait is expressed in both the heterozygote and the homozygote. Although the classical Mendelian formulation requires that the homozygous and heterozygous phenotypes be indistinguishable for true dominant inheritance, it is common practice in human genetics simply to classify a disease or trait as dominant if it is expressed in the heterozygote, whether the homozygote is affected equally or more severely.

METABOLIC INTERFERENCE AND THE + − HETEROZYGOTE

In considering possible molecular models for dominant diseases [1, 2], it became apparent that another form of simple inheritance is possible which is neither dominant nor recessive. In this model, not previously proposed, the heterozygote alone would be affected, while the homozygote for the abnormal gene would have the normal phenotype.

Basically, either of two allelic genes, A and A', gives the normal phenotype, but if present together, they interact to produce a harmful effect and an abnormal phenotype. Figures 1 and 2 show examples of such a mechanism in an enzyme protein and in a structural protein, respectively. Many other mechanisms of harmful interaction between two genes can readily be constructed. Neither A nor A' is really abnormal, since the AA and $A'A'$ homozygotes both have the normal phenotype. A and A' are abnormal only in that their interaction in the same individual, the + − heterozygote, produces a harmful effect.

This situation may be termed *metabolic interference*, the opposite of *metabolic cooperativity*. In the latter phenomenon, two types of abnormal genes interact to produce a normal phenotype. In metabolic interference, on the other hand, two different alleles interact to produce an abnormal phenotype.

INHERITANCE PATTERN OF THE + − HETEROZYGOTE

Consideration of the mating types (figs. 3–6) of such a gene system leads to some surprising predictions. In one pedigree (fig. 3*d*), all children of normal parents are affected no matter how large the family. Although such pedigrees are, in fact, seen, they are usually explained in other ways. For example, such a pedigree may result, very rarely, from autosomal recessive inheritance. Nonpaternity might be suggested with the biological father having a dominant disorder. Alternatively, an intrauterine effect might be suspected.

If such a locus is X-linked (fig. 4), the abnormal phenotype occurs only in females. At times the inheritance appears dominant (fig. 4*a* and *b*) and at times, recessive.

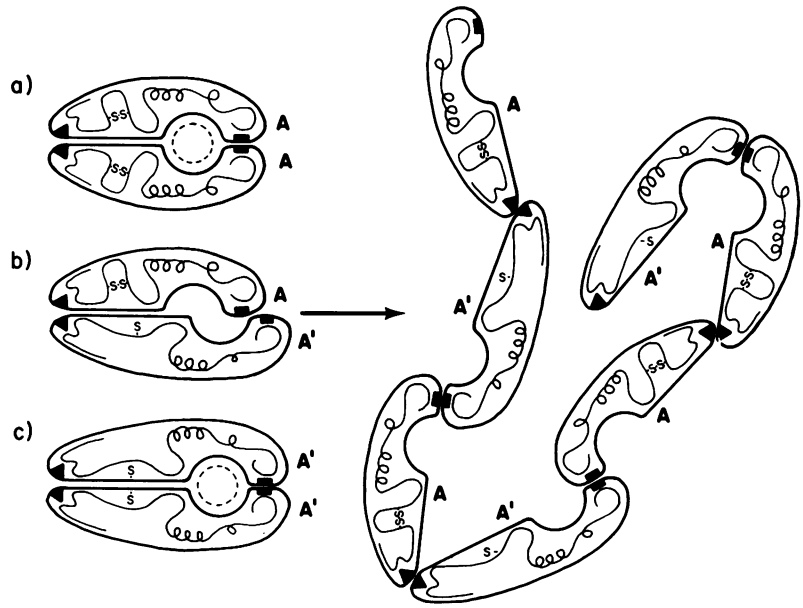

FIG. 1.—Mutation affecting an enzyme protein. *A* and *A'* are allelic genes. Neither the *AA* enzyme nor the *A'A'* enzyme is abnormal, but *A* and *A'* subunits together interact to give low enzyme activity. *a*, *AA* protein is a dimer composed of *A*-subunits produced by *A*-cistron. Active site is shown by *broken line* and subunit binding sites by *solid rectangles* and *triangles*. Homozygotes with *AA* genotype have normal enzyme activity and normal phenotype; *b*, a mutation of *A*-cistron gives allelic *A'*-cistron which produces *A'*-subunits. *A'*-subunits are slightly longer than *A*-subunits, but their subunit binding sites function, and active site region is unaffected. Length change here results from loss of a disulfide bond, but there are many other possibilities. *A'*-subunits still bind to *A'*-subunits, but no active site is formed, and the enzyme is inactive. *AA'* protein is produced by heterozygotes who have decreased enzyme activity levels and abnormal phenotypes. *AA'* heterozygotes could produce some active *AA* and *A'A'* enzymes as well as inactive *AA'* enzyme. However, if the *A*- and *A'*-subunits aggregate and precipitate as they are formed, as shown to the *right* of the figure, the amount of residual active *AA* and *A'A'* enzyme is further reduced toward zero. If the enzyme in question has more than two subunits, then amount of residual active enzyme is reduced still further; *c*, *A'*-subunits bind together to produce a normally functioning enzyme. *A'A'* enzyme is produced by homozygotes for *A'*-allele (*A'A'* genotype), who have normal levels of enzyme activity and normal phenotype.

Surprisingly, such a disorder may appear to be transmitted by an unaffected male ($X_{A'}Y$). An $X_{A'}O$ female (Turner syndrome) would be unaffected. Genetic disorders are known which occur only in females. Some of these are shown in list 1. One explanation for such apparent sex-limitation is that these are X-linked dominant disorders, and that the more severely affected males die in utero. Metabolic interference offers an alternative explanation for some of these disorders.

Those disorders in list 1 which are multifocal (e.g., focal dermal hypoplasia) are explained by the X-linked dominant hypothesis, since mammalian females are mosaics with respect to most X-linked genes according to the Lyon hypothesis [3, 4]. However, multifocal pathology can also be explained by metabolic interference. For example, if the *A* and *A'* subunits interact extracellularly or at the cell surface, then in the female with the *AA'* genotype, the abnormal *AA'* protein and the pathology may be found in

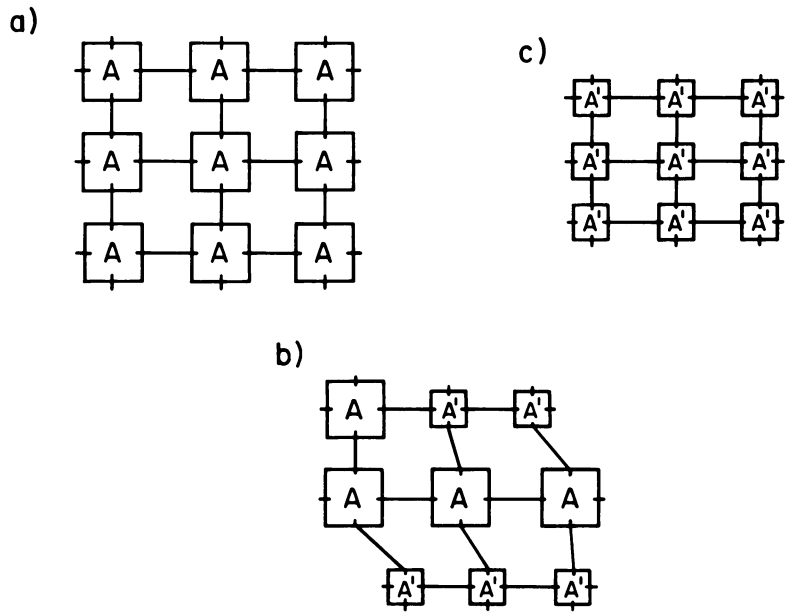

FIG. 2. —Mutation affecting a structural protein. *A* and *A'* are allelic genes. Neither *A*-subunit nor *A'*-subunit alone is abnormal. However, together they interact to produce a harmful effect. *a*, *AA* protein is a multisubunit structural protein composed of *A*-subunits produced by *A*-cistron. This normal protein is produced in individuals homozygous for *A*-cistron (*AA* genotype) who have normal phenotype; *b*, mutation affecting *A*-cistron gives allelic *A'*-cistron coding for *A'*-subunit. *A'*-subunit has different configuration of subunit binding sites, but still binds to *A*-subunit to give an abnormal, malfuntioning *AA'* protein. *AA'* protein is produced by heterozygotes with *AA'* genotype who have abnormal phenotype; *c*, *A'*-subunits bind well with each other to produce a normally functioning *A'A'* protein. *A'A'* protein is produced by individuals with *A'A'* genotype who have normal phenotype.

multifocal distribution at the interface of cell clones producing only *A* subunits and those producing only *A'* subunits.

If the *A'A'* protein is mildly abnormal but less severely abnormal than the *AA'* protein, other interesting pedigrees result (figs. 5 and 6). Both mildly and severely affected individuals appear in the same pedigree (5*b*, *c*, and *d*) mimicking variable expressivity. In the X-linked situation (fig. 6), the pedigrees resemble X-linked dominant inheritance, except that females are more severely affected. In conventional X-linked dominant inheritance, males are more severely affected. The limiting case of both is equal involvement of males and females. List 2 includes some disorders thought to be X-linked dominant but which are not worse in males. These disorders may be explained either by metabolic interference or X-linked dominant inheritance.

Not all of the pedigrees expected for metabolic interference are unusual. The most likely pedigree (fig. 3*a*), in fact, is indistinguishable from autosomal dominant inheritance, even if many generations can be ascertained.

Metabolic interference must be rare if it occurs. There is no heterozygote advantage, as with recessive genes, to increase the gene frequency in a population through natural selection. On the contrary, the selective pressure is against the heterozygote in

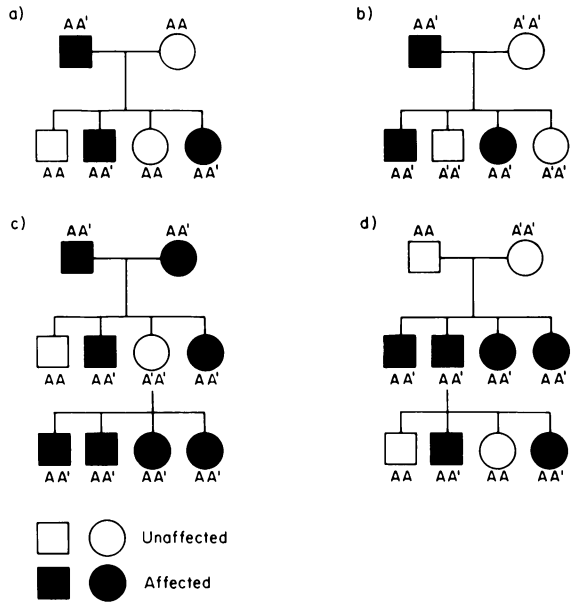

FIG. 3.—Mating types, assuming that: (1) A and A' are autosomal alleles, and (2) A is common, A' is rare. *a*, Indistinguishable from autosomal dominant inheritance; *b*, resembles autosomal dominant inheritance. Apparently "dominant" gene is nonpenetrant in two $A'A'$ children, all of whose offspring will be affected. $A'A'$ mother probably had one or both parents affected and perhaps parental consanguinity as well; *c*, resembles autosomal dominant inheritance. Apparently "dominant" gene is nonpenetrant in one $A'A'$ child, all of whose offspring will be affected (as shown in 3*d*); *d*, all children are affected no matter how large the family. Resembles autosomal recessive inheritance if family is small with only two generations known. Resembles an intrauterine effect except that all children transmit trait as apparent dominant (as shown in third generation). $A'A'$ mother probably had one or both parents affected and perhaps parental consanguinity as well.

metabolic interference. However, the selective disadvantage is no more severe than for conventional dominant inheritance. Consequently, such a disorder may be expected to have a population frequency similar to that of representative dominant disorders.

The unusual pedigrees shown would probably be overlooked in practice for three reasons. First, conventional dominant and recessive inheritance are likely to be the only inheritance patterns considered. Second, all pedigrees shown can be explained as unusual examples of conventional dominant or recessive inheritance. Third, in human genetics, definite conclusions about inheritance pattern are often difficult to reach because of small family size, adoptions, nonpaternity, infant mortality, and limited knowledge of earlier generations.

Table 1 shows the relative frequencies of the matings shown in figures 3–6, assuming that the gene frequency of A' is 1×10^{-4}. Clearly, only three of these matings are common enough to occur repeatedly in human populations. The most common of these, $A'A \times AA$, gives a pedigree indistinguishable from autosomal dominant inheritance (fig. 3*a*). The other two, $X_AY \times X_AX_{A'}$ (fig. 4*a*) and $X_{A'}Y \times X_AX_A$ (fig. 4*d*), are nearly as common and more likely to be recognized as resulting from metabolic interference since their consequences are highly unusual (a disorder

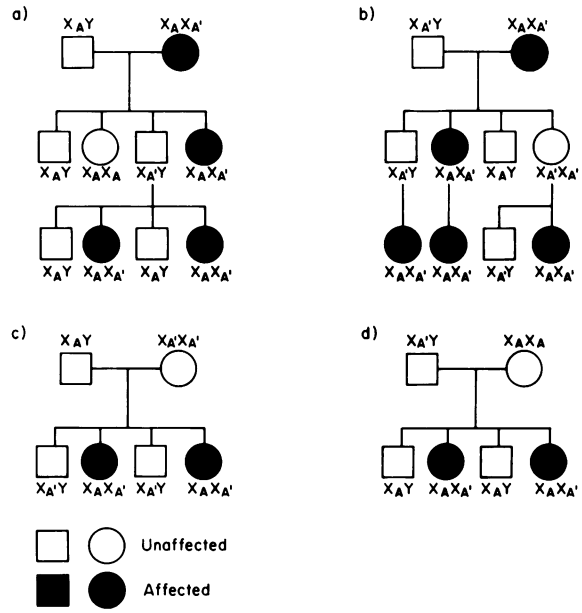

FIG. 4. —Mating types, assuming that: (1) A and A' are X-linked alleles, and (2) A is common, A' is rare. *a*, Resembles autosomal dominant inheritance, but only females are affected. Trait appears to be nonpenetrant in one unaffected son who transmits the trait to all of his daughters, but to none of his sons; *b*, resembles autosomal dominant inheritance, but only females are affected. Trait appears to be nonpenetrant in unaffected son and unaffected daughter who transmit trait to all of their daughters, but to none of their sons; *c*, resembles autosomal recessive inheritance, but only females are affected. All sons are unaffected and transmit trait to all of their daughters; *d*, resembles autosomal recessive inheritance, but only females are affected. They will transmit trait to half of their daughters and none of their sons.

occurring only in females, apparently either dominant or recessive, and apparently passed through unaffected males). Four other matings have lower frequencies (1×10^{-8} to 4×10^{-8}) and would occur very rarely in the human population. However, they would be more likely to be recognized as resulting from metabolic interference since their consequences are so unusual (a disorder occurring in all members of a large sibship with normal parents). One mating is too infrequent to be expected in human populations. However, these pedigrees might occur more commonly if: (1) non-random mating occurred; (2) if the fitness of the + − heterozygote were only slightly reduced; or (3) the frequency of A' were increased by founder effect or genetic drift.

EFFECT OF THE LYON HYPOTHESIS

The pedigrees of figure 4, which show apparently dominant (fig. 4*a* and *b*) or apparently recessive (fig. 4*c* and *d*) inheritance of a disorder limited to females, depend on the fact that females alone may have both the A and the A' alleles since they alone have two X chromosomes. This is true in the very early development of the human embryo. However, early in development, perhaps between 12 and 16 days, the major portion of one X chromosome in each cell is inactivated according to the Lyon

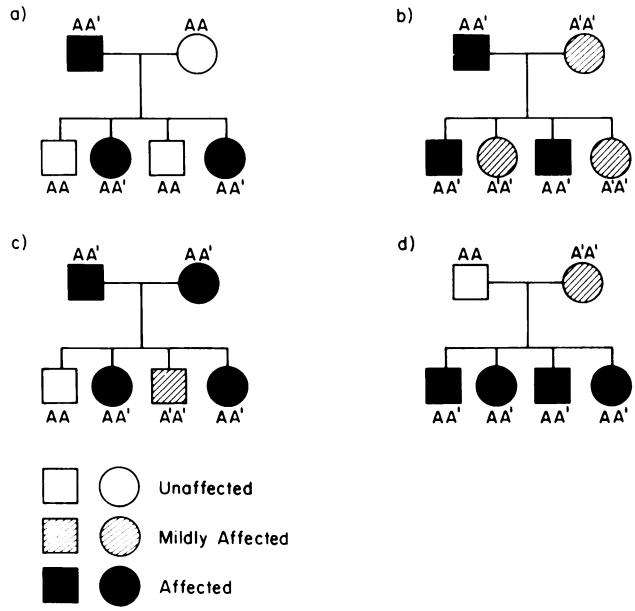

FIG. 5.—Mating types, assuming that: (1) A and A' are autosomal alleles, (2) A is common, A' is rare, and (3) $A'A'$ protein is mildly abnormal but less so than AA' protein. *a*, Indistinguishable from autosomal dominant inheritance; *b*, resembles autosomal dominance with variable expressivity. Also compatible with autosomal recessive inheritance; *c*, resembles autosomal dominance with variable expressivity; *d*, resembles autosomal dominant inheritance with variable expressivity.

hypothesis [3, 4]. A small portion of the X chromosome may escape inactivation [5]. The Lyon hypothesis places certain limitations on disorders showing the inheritance pattern of figure 4. First, the X-linked gene in question may be located on the non-inactivated portion of the X chromosome since each cell contains two functioning copies of these genes. Second, the gene may affect the germ cells of the female since these cells are not subject to X-inactivation and retain two functioning X chromosomes. Third, the gene may affect tissues, such as muscle, with multinucleate cells. Thus, even though each nucleus may contribute only the A allele or only the A' allele, the cell will have both A and A' gene products, and metabolic interference may occur. Fourth, the gene may code for factors involved in cell-to-cell interaction, such as cell surface receptors or recognition markers. In this way, a cell expressing only the A allele on its surface may interact with a cell expressing only the A' allele on its surface to produce a harmful effect. This interaction would occur most prominently at interfaces where A-clones abut A'-clones and might produce a multifocal pathology. Finally, the gene may code for a product which is secreted into the extracellular space. In this way, the products of the A gene and A' gene would meet and could interact harmfully, perhaps by exchanging subunits or perhaps by another mechanism. In addition, some gene products are first secreted into the extracellular space and then taken up again by the cell for their action to occur. In this way, a cell could produce only the A or A' gene product but contain both for metabolic interference to occur.

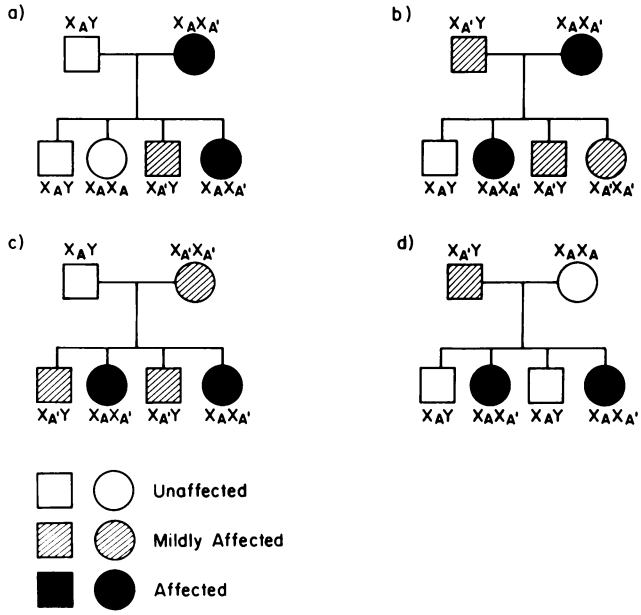

FIG. 6. —Mating types, assuming that: (1) A and A' are X-linked alleles, (2) A is common, A' is rare, and (3) $A'A'$ protein is mildly abnormal but less so than the AA' protein. *a*, Resembles autosomal dominance with milder involvement in males. Resembles X-linked dominance except that males are not more severely affected; *b*, resembles autosomal dominance with milder involvement in males; *c*, resembles autosomal dominance with milder involvement in males. Resembles X-linked dominance except that males are not more severely affected; *d*, resembles autosomal dominance with milder involvement in males. Resembles X-linked dominance except that males are not more severely affected.

THE NON-ALLELIC CASE

For all pedigrees shown, the assumption is that metabolic interference is occurring between two alleles of a single gene. This assumption is not necessary. It is quite possible that two different non-allelic genes, which themselves cause no abnormality of the phenotype, could interact when present together to cause a harmful effect and an abnormal phenotype. The inheritance patterns resulting from the metabolic interference of non-allelic genes, in general, resemble those shown earlier.

At least two differences should be mentioned. If A and B are non-allelic genes, and the uncommon allele B' interacts harmfully with A (or with A', an allele of A), an individual may now have a double dose of the B' allele and still have one or two copies of A (genotype AB'/AB'). Consequently, such an individual in the most probable mating ($AB'/AB' \times AB/AB$) would produce all affected (AB'/AB) children. In this way, a mating of an affected individual and an unaffected individual could produce all affected children, no matter how many children were produced (cf. fig. 3). Such pedigrees are occasionally seen and are attributed to a dominant gene and "bad luck." Another difference in metabolic interference between non-allelic genes is that in the X-linked case males may be affected (cf. fig. 4).

LIST 1

DISEASES OCCURRING ONLY OR LARGELY IN FEMALES

Myopathy limited to females (16060, 30995)*
Congenital cataract with microcornea or slight microphthalmia (30230)
Agenesis of the corpus callosum with chorioretinal abnormality (30405)
Focal dermal hypoplasia (Goltz syndrome) (30560)
Incontinentia pigmenti (30830)
Oral-facial-digital syndrome (31120)
Sacral defect with anterior sacral meningocele (31280)
Wildervanck syndrome (cervico-oculo-acoustic syndrome) (31460)

* Five digit nos. refer to listing in McKusick's catalog. (MCKUSICK VA: *Mendelian Inheritance in Man*, 5th ed, Baltimore, Johns Hopkins Univ Press, 1978)

EVIDENCE FOR METABOLIC INTERFERENCE

What evidence supports the concept of metabolic interference? It can be argued that since it appears to be possible, it is bound to occur in a system as complex as the mammalian genome. However, at least three types of observations may support the hypothesis.

Pedigree Evidence

As mentioned earlier, the most likely pedigree pattern for metabolic interference (fig. 3*a*) is identical to that of simple autosomal dominant inheritance. Although the biochemical mechanisms of most autosomal dominant disorders are unknown, and although any of these disorders may, in fact, result from metabolic interference, such pedigrees do not provide specific evidence for the existence of metabolic interference.

Other less common pedigree patterns do give support to the concept of metabolic interference. A number of disorders (list 1) are known to occur invariably or almost invariably in females. X-linked dominant inheritance with lethality in affected males is the present explanation for these disorders, and no doubt accounts for some. Metabolic interference between alleles of an X-linked gene (fig. 4) offers a second explanation for disorders limited to females. A striking pedigree for oral-facial-digital syndrome (list 1) has been published [6], which corresponds with the predictions of metabolic interference between alleles of an X-linked gene. In this family, oral-facial-digital syndrome was apparently passed from an affected woman through three unaffected sons to nine affected granddaughters (cf. fig. 4*a*). These three unaffected sons passed on the trait to all of their daughters but to none of their sons, as predicted for metabolic

LIST 2

DISEASES COMPATIBLE WITH X-LINKED DOMINANCE BUT NOT WORSE IN MALES

Albright hereditary osteodystrophy (30080)*
Hyperuricemia, ataxia, deafness (30720, 23995)
Manic depressive psychosis (30920)
Pterygium syndrome (X-linked form) (31215)

* Five digit nos. refer to listing in McKusick's catalog. (MCKUSICK VA: *Mendelian Inheritance in Man*, 5th ed, Baltimore, Johns Hopkins Univ Press, 1978)

TABLE 1

FREQUENCY OF MATING TYPES

Mating type	Approximate frequency of mating
A) A′ is autosomal with frequency 1×10^{-4}	
$AA' \times AA$	4×10^{-4}
$AA' \times A'A'$	4×10^{-12}
$AA' \times AA'$	4×10^{-8}
$AA \times A'A'$	2×10^{-8}
B) A′ is X-linked with frequency 1×10^{-4}	
$X_A Y \times X_A X_{A'}$	2×10^{-4}
$X_{A'} Y \times X_A X_{A'}$	2×10^{-8}
$X_A Y \times X_{A'} X_{A'}$	1×10^{-8}
$X_{A'} Y \times X_A X_A$	1×10^{-4}

NOTE. —Frequency of *A′* is assumed to be 1×10^{-4}, and frequency of matings' (figs. 3–6) calculation is based on Hardy-Weinberg distribution. Matings are listed in order shown in figures.

interference. All ten affected individuals in the pedigree were females. This pedigree cannot be explained by X-linked dominance with male lethality. To say that this is a "dominant disorder with sex-influenced expressivity or penetrance" is not an explanation at all. Both X-linked dominance with male lethality and metabolic interference between alleles of an X-linked gene are mechanisms for "sex-influenced expressivity or penetrance." Another remarkable pedigree [7] compatible with metabolic interference is that of a myopathy limited to females and occurring in four females through three generations. Such a disorder occurring in muscle is of particular interest as discussed above.

List 2 contains another group of disorders which may provide examples of metabolic interference. These are disorders in which inheritance is compatible with X-linked dominance but in which males are not more severely affected. They may be explained equally well as examples of X-linked dominance or as examples of metabolic interference between alleles of an X-linked gene. Males are usually more severely affected in the former; females in the latter (cf. fig. 6). Equal involvement in males and females is the limiting case of both mechanisms.

Finally, pedigrees are occasionally seen in which all members of a large sibship are similarly affected. If the parents are unaffected, this is assumed to be an example of autosomal recessive inheritance and "bad luck." However, this could represent metabolic interference (cf. fig. 3*d*). In the same way, involvement in one parent and all members of a large sibship is occasionally seen and attributed to autosomal dominant inheritance and "bad luck." However, this could also represent metabolic interference (cf. THE NON-ALLELIC CASE).

Animal Models

Sturtevant described in *Drosophila melanogaster* [8] a case of harmful interaction between two genes. The first was prune (*pn*), an X-linked recessive gene affecting eye

color; the second was Prune-killer or Killer of Prune (*K-pn*), which was autosomal on chromosome III. *K-pn* had no known phenotypic effect either in single or double dose except to cause the death of all prune flies carrying it—this effect being dominant. Males that were *pn*: *K-pn* died at the end of the second larval instar without any gross phenotypic abnormalities. *K-pn* did not interact with eye-color genes other than *pn*. Although the basis of this harmful interaction is unknown, this is a possible example of metabolic interference between two non-allelic genes. The interference could result from a mechanism in which two gene loci contribute subunits to a multisubunit protein (as in figs. 1 and 2) or from some other mechanism. Interestingly, this phenomenon in *Drosophila melanogaster* is somewhat reminiscent of multiple spontaneous abortions occurring in human families. Some of these pedigrees resemble figure 3*d*.

Interspecies Hybrids

Although the phenomenon of "hybrid vigor" is well known, in some instances hybridization between species may produce disease. An example of this [9, 10] is the development of melanomas in platyfish-swordtail hybrids. Although the genetic basis for this phenomenon appears to be complex and the action of these genes at the biochemical level is not understood in detail, metabolic interference may have a role in this type of phenomenon. If the A allele occurs in one species and the A' allele in another, the hybrid containing both A and A' alleles could be harmfully affected if metabolic interference occurs between the two alleles. Additionally, it is possible that metabolic interference could have a role in infertility between species and in the evolutionary phenomenon of species differentiation (cf. fig. 3*d*).

PROVING THE EXISTENCE OF METABOLIC INTERFERENCE

At least four approaches may be useful in trying to prove that such a mechanism of inheritance exists. A definitive approach would be to purify the A and A' subunits and show directly that the protein produced by aggregation of A subunits only or A' subunits only is normal in structure or function, while a mixed protein with A and A' subunits is abnormal in structure or function. Obviously, this approach depends on knowing which protein to study.

A second approach is to use tissue culture techniques to demonstrate metabolic interference. This requires that cells such as cultured skin fibroblasts from an affected individual with AA' genotype show an abnormality in culture (enzyme deficiency, cytopathic effect, inclusion bodies, etc.), and that an informative family such as that of figure 3*d* be available for study. In this situation, cells from the unaffected parents (genotypes AA and $A'A'$), showing no abnormality in culture, could be tested for metabolic interference. AA cells and $A'A'$ cells could be co-cultivated or fused to produce binucleate cells with both types of nuclei. The appearance of the characteristic abnormality on co-cultivation or fusion of parental cells would constitute evidence for metabolic interference.

A third approach also uses tissue culture techniques to study the X-linked case (fig. 4). Again, an informative family and a tissue culture marker are required. Cloning the cell culture of an affected female should give two kinds of clones, normal and abnormal, if the female limitation is due to an X-linked gene lethal in males. If no

abnormal clones could be found after an extensive search, even though the abnormality could be demonstrated in the uncloned cells, this finding would be evidence for metabolic interference. Alternative explanations, however, would be that (1) the abnormal clones had died out due to adverse selective pressure, and (2) the disorder was not, in fact, caused by an X-linked gene.

A fourth approach has already been discussed: to search for unusual pedigrees which are compatible with metabolic interference and difficult or impossible to explain by other means. In considering such unusual pedigrees, it is important to keep in mind the possibility of a new mechanism, such as metabolic interference, and not to jump to the premature conclusion that the pedigree represents an unusual case of conventional dominant or recessive inheritance.

CONCLUSIONS

Three conclusions can be drawn from this discussion. First, another form of simple inheritance is possible, which is neither dominant nor recessive. Second, metabolic interference is most likely to be recognized as: (1) a disorder limited to females (list 1), apparently dominant or recessive, especially a disorder passed to affected females through unaffected males; (2) a disorder occurring in all members of a large sibship with normal parents; (3) a disorder occurring in all members of a large sibship with one parent similarly affected; (4) an apparently dominant disorder with females more severely affected than males; (5) an apparently X-linked dominant disorder in which males are not more severely affected (list 2); or (6) any autosomal dominant disorder. And third, not all unusual pedigrees need be interpreted as unusual examples of dominant or recessive inheritance. The complexities of the mammalian genome are largely unexplored, and new genetic mechanisms may yet be found.

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A course, GENETICS IN CLINICAL ONCOLOGY, will be offered on September 22 and 23, 1980, in New York City by the Laboratory of Genetics, Department of Pathology, Memorial Hospital for Cancer and Allied Diseases. The course will provide current knowledge of genetics as it pertains to clinical oncology. Topics will include: chromosome changes in leukemia and solid tumors, heredity in predisposition to cancer, etiology and nature of cancer, genetic counseling in cancer, and indications for genetic and cytogenetic work-up. Approved for 15 credit hours in Category I of the AMA Physicians Award. The $200 fee includes registration. Co-directors: R.S.K. Chaganti, PhD and James L. German, III, MD. For more information, write to: Dr. R.S.K. Chaganti, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021. (212) 794-7100.